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Cerebral Cortex: Function and Development

Meeting Review

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"Structure et Function dans le Systeme Visuel" was the title given to the first Institut National de la Santé et de la Recherche Médicale (INSERM) symposium held on this topic in Lyon in September 1986. Nine years later, its successor was held in the same place. What has changed? Well, the Salle Moliere has had a face-lift, and it would be difficult to think of a finer venue for a meeting of about 150 people. It is also salutary to spend 4 days debating science in a chamber so conspicuously dedicated to the arts. Fifteen of the speakers or coauthors at the first meeting were presenting their work again, and although some of us could be said to need a face-lift, there was a reassuring novelty about many of their contributions. Some old dogs do learn new tricks! The title, "Cerebral Cortex Function and Development," was much broader than that of its predecessor, but the proceedings, as often happens, revealed a narrower perspective, most of the contributions dealing with the visual system, with far fewer, albeit distinguished, excursions into somatosensory and language processes.

It is particularly illuminating to compare the programs of the two meetings, for although their overall aims were similar—structure and function—the ways in which questions are tackled have shifted substantially in 9 years. Whereas about half of the platform presentations and posters in 1986 were devoted to the structure of the retina or to the classical receptive field properties of single neurons in the visual pathways, in 1995 the structure of the retina was barely mentioned, the emphasis on information processing was computational, model building was popular, the human (as opposed to feline or simian) cerebral cortex was frequently mentioned, functional neuroimaging reared its controversial head, and the studies of neural development embraced chemistry and dishes.

Cortical Development: Early Events

One of the foremost questions about the development of the cortex is how its complex yet orderly connections arise. It is the same question asked by Roger Sperry about sensory projections half a century ago. How are specific pathways from the thalamus to a particular cortical area and the precise synaptic connections within and between areas (which enable a cortical area to carry out specific functions) established? While we are far from a complete answer to these questions, it was clear from the meeting that a glimmer of an answer is emerging.

The earliest event in cortical development includes the generation of cells in the ventricular zone that are destined for different cortical layers. Cortical layers are generated in an inside-out fashion, with cells destined for the deepest layer (layer 6) born first and more superficial cells born progressively later from the same progenitor cell. Cells are committed to a laminar "fate" before birth, though cells born at a particular location in the ventricular zone can end up in widely separate parts of the cortex, and hence belong to different cortical areas (Goodman and Shatz, 1993).

Targeting and innervation of cortex by thalamocortical axons proceeds as cortical laminae form, and this is the key event in the demarcation of cortex into individual areas. The issue has been studied most extensively in the rodent somatosensory projection. Herbert Killackey (University of California, Irvine) showed that axons from the ventrobasal nucleus specifically target somatosensory cortex from the outset. Furthermore, the projections appear to be reasonably precise in terms of their overall topography. How such specific targeting by thalamic axons is achieved remains unanswered. It is clear that thalamic axons recognize specific cues at the appropriate cortical locus: one possibility is that the information for establishing areal identity resides in the ventricular zone itself (Rakic, 1988), which thereby establishes not only the radial (laminar) distribution of cells but also at least a crude tangential (areal) map for the developing cortex. A related possibility is that area-specific markers appear somewhat later in the subplate (a transient, early generated population of cells in the white matter just below the cortical layers). However, molecular markers that uniquely demarcate specific areas of the ventricular zone, the subplate, or the cortex have not yet been reported.

It is also likely that some means of interaction exists between ingrowing thalamic axons and the developing cortex. Barbara Finlay (Cornell University) reported that lesions that reduce the size of thalamic nuclei also reduce the size of their target cortical areas, suggesting an instructive role for the thalamus in the specification of cortex. Experimental approaches examining the development of thalamocortical projections in vitro give promise of a molecular analysis of the problem. Jurgen Bolz (INSERM) showed that specific membrane-bound molecules regulate the termination of thalamic axons in appropriate layers, and this laminar specificity does not depend on electrical activity. In contrast, the arborization of thalamocortical axons measured in vitro is influenced significantly by activity (Kimon Angelides, Baylor University).

Activity-Dependent Development and Plasticity

The effect of neural activity on development of projections has been extensively studied in the visual pathway. It has long been known that abnormal activity induced by brain damage or environmental interventions such as dark rearing and eye closure can disrupt normal development of

the visual cortex. While developmental plasticity in the mammalian brain has been established for over a quarter of a century, an emerging contemporary idea is that of adult plasticity. While no one believes that the factors governing development are identical to those that underlie everyday and adult "plasticity," such as learning and memory, there is now substantial interest in synaptic modifiability and the extent to which early development and the changes that underlie adult learning share common mechanisms. Although the mechanisms by which neural activity influences cortical development and subsequent alterations in cortical properties remain obscure, the conference at least aired some of their emerging properties.

Michael Stryker (University of California, San Francisco) demonstrated the ways in which pre- or postsynaptic activity could influence thalamocortical arbors. Blocking retinal activity with tetrodotoxin in kittens prevents the segregation of geniculocortical axons into ocular dominance columns. Hubel and Wiesel had first shown that monocular lid suture in kittens during a "critical period" caused cortical cells to be dominated by the open eye. The surprising finding now is how rapidly the anatomical effects of lid suture, including a reduction in size of axon arbors related to the deprived eye, can occur. Interestingly, if postsynaptic cells are prevented from firing action potentials, axons from the nondeprived eye have smaller arbors in cortex, arguing that pre- and postsynaptic activity together regulate axon arbor size and synaptic connections. Dennis O'Leary (Salk Institute) showed that in the rat somatosensory cortex as well, pre- and postsynaptic activity together influence thalamocortical arbors and cortical connectivity, for blocking postsynaptic activity causes thalamic afferents to spread and activate neurons in inappropriate "barrels."

That neuronal activity does play a major role in specifying neuronal connections now seems incontrovertible. The mechanisms by which activity affects thalamocortical arbors and synaptic connections are unresolved. In reviewing the evidence, Wolf Singer (Max-Planck Institute, Frankfurt) argued that it is temporal patterning rather than the level of activation that is important, for example, in the development of the intracortical tangential connections that are widely believed to contribute to a wide range of receptive field properties of visual cortical neurons. Conditions such as strabismus or monocular deprivation prevent the customary synchronization (meaning phase of cell discharges and not just their rate) that binds and reinforces the anatomical and functional connection of certain populations of cells and not others. Such conditions do not merely untie the functional roles of the two eyes; the deprived eye has fewer cortical connections than its partner because it was unable to provide or sustain correlated cortical activity. Its cortical input may not simply be "weak"; rather, it is disorganized. For example, if the appropriate intracortical connections between cortical columns representing widely separated but collinear contours have not been selected and strengthened, a grating might appear to be wavy and fragmented but lacking the Gestalt of a whole figure, as occurs in strabismic amblyopia.

Mriganka Sur (Massachusetts Institute of Technology) also provided evidence that the pattern of afferent activity (rather than simply the amount of activity) is likely to be the key determinant of synaptic efficacy during cortical development. This is demonstrated by experiments in which projections from the retina are routed to the auditory thalamus in newborn ferrets, so that visual rather than auditory inputs activate auditory cortex. Primary auditory cortex in "rewired" animals develops orientation-selective receptive fields and a map of visual space typical of visual cortex, in spite of highly convergent and divergent projections from the auditory thalamus, suggesting that spatial and temporal correlations in input activity cause selective strengthening of specific sets of synapses from a broad set available anatomically.

A basic hypothesis arising from the observations described above is that activity-dependent sharpening of connections is akin to a "Hebbian" process, which is that temporal correlation between pre- and postsynaptic cells leads to a strengthening of the synapses between them, while lack of correlation leads to a weakening of synapses. Cellular correlates of Hebbian synapses in developing cortex are the subject of intense study. Recent experiments demonstrate that activity-dependent strengthening of synapses akin to long-term potentiation (LTP) in the hippocampus indeed occurs during an early critical period of development at thalamocortical synapses in rats, both in the barrel cortex (Crair and Malenka, 1995) and in visual cortex (Kirkwood et al., 1995).

How do correlated activity and synaptic strengthening lead to consolidation and growth of axon arbors (or conversely, synaptic weakening and axonal retraction)? The chemical and molecular events that underlie neural development, and their dependence on neural activity, remain almost totally unknown. Lamberto Maffei (Consiglio Nazionale delle Ricerche, Pisa) described experiments showing that neurotrophic growth factor (NGF) applied during the "sensitive period" prevents the anatomical and functional effects of monocular deprivation in the dorsal lateral geniculate nucleus (dLGN) and the striate cortex, as well as the behavioral effects of binocular deprivation. It also preserved the high proportion of binocular cells that characterize the newborn visual cortex. Not surprisingly, antibodies to NGF produced deleterious effects on visual acuity and binocularity as well as stunting the growth of LGN neurons. Why some investigators have failed to find evidence for the role of NGF in development is an unresolved problem. In visual cortex, competitive restructuring of axons from the two eyes during the critical period may be regulated by other neurotrophic factors as well, such as brain-derived neurotrophic factor (BDNF) (Singer; Cabelli et al., 1995). An important role for serotonin (5-HT) in the development of somatosensory cortex in rats was described by Robert Rhoades (University of Toledo). Serotoninergic axons form a pattern of cortical connections similar to that of the thalamocortical axons but appear a day later and as mysteriously disappear 2 weeks later. During this brief life span, thalamocortical axons transiently express 5-HT receptors, mediating prominent inhibition on thalamocortical transmission. Depleting this 5-HT by subcutaneous 5,7-dihydroxytryptamine constricts the terminal arborization of the thalamocortical afferents rep-

resenting the vibrissae, an effect reminiscent of that of N-methyl-D-aspartate on the developing retinotectal terminals of frogs (Cline et al., 1987).

Casting the question of activity-dependent development in terms of function, Colin Blakemore (University of Oxford) reviewed classical work on the postnatal development of the primate visual system. Knowing the precise time course of this protracted period of development is essential to understanding why the effects of disorders like strabismus are age dependent. Visual receptive fields in the thalamus and striate cortex have poor spatial resolution and contrast sensitivity (as does visual behavior) for many months after birth and do not reach adult levels for 2 years in monkeys. The improvement appears to reflect passive anatomical changes in the eye, and monocular deprivation has few if any measurable physiological effects in the eye or the thalamus. However, there is increasing evidence for activity-dependent processes in shaping and maintaining the pattern of input to the striate cortex, where the effects can be seen at the very first stage of the thalamocortical input. Whereas 10 years ago it was thought that the period during which the properties of the cortex and the quality of vision could be altered by environmental changes lasted for probably only a few months after birth, it is now clear that cortex can be modified well beyond the classical sensitive period (see below). But some of the simplest problems remain unresolved. For example, there is little evidence that the grossly impaired vision through a visually deprived eye is in any way offset by improved vision via the nondeprived eye and the cortical territory it has "captured" from its partner. Perhaps we are too dependent on a small range of psychophysical tasks in assessing the hypernormal monocular vision that might have been expected (Nicholas et al., 1995).

Development of Intracortical Connections

Similar to thalamocortical connections, connections between cortical areas are also broadly precise early in development, though again there is evidence for later sharpening by activity. David Price (University of Edinburgh) showed that the basic patterns of clustering and topography that mark ipsilateral projections between areas of the cat visual cortex are present at early postnatal ages. However, the density of projections gradually declines with age, and an appropriate laminar distribution emerges. In monkeys, too, Henry Kennedy (INSERM) showed that the functional segregation of processing streams and topographic organization of ipsilateral visual cortical pathways appears to be present very early in development and is probably genetically specified rather than activity dependent. Among corticortical projections, callosal projections that link visual areas in one hemisphere to areas in the opposite hemisphere perhaps sharpen the most during development. Giorgio Innocenti (University of Lausanne) argued that the substrate for sharpening may be the geometry of branching and progressive differentiation of callosal axon arbors. Callosal axons branch extensively below the cortical plate but enter the cortex at specific, topographically appropriate loci.

Extensive sculpting of projections during development, including directed growth at appropriate loci and retraction of inappropriate projections, is demonstrated by long-range horizontal projections within primary visual cortex of cats (Edward Callaway, University of Colorado). These projections are the intra-areal axonal terminations of pyramidal cells in the superficial layers; in adults, they form distinct clusters and link cells with similar orientation preference. This pattern develops from an initially more diffuse or more ramified arrangement. As orientation-selective cells develop (a process dependent on neuronal activity), branches in the appropriate orientation domains arborize to form clusters while other branches retract.

Cortical Dynamics

The developmentally generated pattern of thalamocortical and intracortical projections in adults, when viewed at the level of single axon and dendritic arbors, still allows for an almost unimaginable lack of precision. A single cortical cell might typically receive 5,000–10,000 synapses on its dendrites, very few of which are from any one presynaptic axon. Similarly, single thalamocortical axon arbors spread widely, as shown by Edward Jones (University of California, Irvine), and a given axon might potentially contact several hundred postsynaptic cortical cells. When one adds to the spread of thalamocortical arbors the spread of horizontal intracortical axon arbors, the potential convergence and divergence of activity in cortex is magnified even further. Specific physiological response features of neurons would require either that all these synapses are prespecified, which almost no one believes (largely because they cannot conceive of a mechanism that constructs the necessary developmental specification), or that an appropriate set of synapses is selected physiologically from the potentially large number present anatomically. If the latter is true, it should be possible to change the selected set of synapses by altering the relative strength of a subpopulation. The demonstration of rapid plasticity and dynamic alteration in receptive field properties even in the adult primary visual cortex indicates that this is indeed the case.

A single neuron in primary visual cortex clearly receives and integrates inputs not only from the thalamus but also from other cortical neurons, some of which can lie many millimeters distant and represent quite distinct regions of visual space. If one includes descending inputs from higher cortical areas, the potential region of spatial integration by such a "lower order" cortical neuron can be extensive. A convenient metaphor might be that inputs to a cell resemble an iceberg: cells have a large subthreshold zone of activation, and while a spike response might be elicited by stimulating only a small central portion of this space, the remaining portion could modulate the spike output in significant ways. In fact, Charles Gilbert (Rockefeller University) showed that adding oriented stimuli in the receptive field periphery changes the orientation selectivity of the center in a subtle fashion, a mechanism that can explain perceptual phenomena such as the "tilt effect." In addition, decreasing the level of central activation with an "artificial scotoma" can cause outer portions of the visual field to drive the cell, thereby enlarging the cell's "receptive

field." An alternative view, expressed by Ralph Freeman (University of California, Berkeley), is that there is a change in overall responsiveness of the cell due to short-term adaptation, rather than an increase in receptive field size.

More generally, the view of a receptive field as a rigidly defined construct is being altered by these findings: a cell's response to a stimulus within its receptive field can be altered by the presence of other stimuli outside, including some that can be quite distant. These findings constitute the first level of complexity and conditionality with respect to neuronal integration in cortex. Responses of neurons in higher visual areas are of course influenced not only by sensory stimuli but also by attention, motivation, and other determinants of behavior.

Plasticity in Adult Cortex

The idea of a single, well-defined critical period during which the cortex is sensitive to external input (but is insensitive later) is being radically redefined by the demonstration that even the adult cortex has the capacity for reorganizing extensively when peripheral inputs are removed or altered. The attack on "ageism" now has plasticity in its sights!

Short-term, rapid changes in responses based on stimulus context can be explained by rapid alterations in the excitability of neurons and neural circuits. In addition, several investigators have now shown that long-term alterations in input activity can lead to major changes in adult cortex. Lesions of the retina lead to a remapping of the deprived cortex, so that cortical neurons acquire new receptive fields based on inputs from intact regions of retina. The remapping could be based either on unmasking and potentiation of preexisting connections or on sprouting of axon collaterals from intact cortex into denervated cortex (Gilbert). The new receptive fields have strikingly normal properties, including orientation tuning, spatial frequency tuning, and direction selectivity (Yuzo Chino, University of Houston), suggesting that the reorganization could be functionally adaptive.

In the somatosensory cortex, where changes in cortical maps following peripheral nerve section were first reported (Merzenich et al., 1983), there are significant topographic irregularities in the map after peripheral nerves to the hand are cut and subsequently allowed to regenerate in adult monkeys. However, Sherre Florence (Vanderbilt University) demonstrated that, after nerve cut and regeneration in fetal monkeys, the topographic organization of the map is remarkably normal. Yet anatomical studies indicate that projection patterns from the hand to the dorsal column nuclei are disordered and topographically irregular regardless of the age of nerve cut. Thus, the creation of a topographically ordered map of the hand in somatosensory cortex after nerve cut and regeneration requires mechanisms (the capacity for cortical or subcortical sprouting, or for strengthening particular synapses from anatomically scrambled projections) that are present in fetal monkeys but not in adults. In general, more extensive changes are possible after peripheral manipulation in the developing brain than in the adult. Consistent with this finding, peripheral injuries in adults have more serious behavioral consequences than similar injuries in early life.

Indeed, some behavioral consequences of peripheral lesions or injury in adults are maladaptive and include phantom limb phenomena and gross spatial mislocalization of sensory events. But Michael Merzenich (University of California, San Francisco) showed that cortical changes can also accompany or even underlie skill acquisition and learning. Repetitive stimulation of a monkey's hand across the fingers, in a direction orthogonal to the usual direction of stimulation during normal use, leads to the appearance of single neuron-receptive fields that have components on two or more fingers, a situation rarely observed in normal monkeys. The cortical map is reorganized significantly in a fashion instructed by the stimulus regimen. Thus, plasticity in cortical representations enables cortical networks to represent or even exaggerate behaviorally relevant, spatiotemporally complex inputs. Again, the pattern of input activity appears to be crucial for selecting and strengthening specific sets of cortical (or spinal) synapses, and such strengthening might form the basis for learning-related plasticity.

Cortical Circuits and Computations

A key function of cortical circuitry is to create new properties from simpler inputs. This property is illustrated superlatively by "orientation-selective" neurons of the visual cortex. Hubel and Wiesel showed that neurons in the primary visual cortex of cats and monkeys respond best to oriented slits or bars of light. Orientation selectivity is created in the visual cortex, for neurons of the visual thalamus, which provide the major input to neurons of the primary visual cortex, are not orientation selective. Thalamic neurons, like retinal ganglion cells whose axons form the projection from eye to brain, respond best to spots of light. How orientation selectivity arises in visual cortex has remained an unsolved problem (despite what the textbooks say) in cortical neurophysiology since it was first posed some 35 years ago. It seems the problem is now close to being solved, thanks to a confluence of ideas from neurophysiology, neuroanatomy, and computational neuroscience.

The earliest proposal for the generation of orientation selectivity in visual cortex came from Hubel and Wiesel themselves. They suggested that an aligned array of thalamic neurons would confer orientation selectivity upon a cortical cell upon which the thalamic axons converged. This simple thalamocortical feed-forward model is consistent with many properties of cortical neurons, including the fact that excitatory postsynpatic potentials are tuned to the cell's best orientation, as showed by David Ferster (Northwestern University), and that thalamic axons recorded at a cortical locus have their receptive fields lined up along the axis of orientation of cortical cells at that locus (Stryker). At the same time, the model leaves several properties unexplained. In particular, Ulf Eysel (Ruhr University, Bochum) provided evidence that intracortical inhibition can sharpen orientation selectivity, and others have shown that orientation tuning of cells remains invariant with increasing stimulus contrast. The last feature, also

known as contrast gain control, can possibly be explained by an addendum to the Hubel–Wiesel model in which responses of cortical cells are pooled and subsequently used to divide and thus normalize (or scale) responses (David Heeger, Stanford University).

A rather different solution to the problem of orientation tuning starts with the anatomical observation that thalamic neurons provide only a minority of synapses onto cortical cells, even in layer 4. In contrast, intracortical excitatory synapses form the vast majority of synapses onto other cortical neurons, while intracortical inhibitory synapses make up the rest. A model in which recurrent intracortical excitation amplifies and sharpens mild orientation bias in thalamic inputs to cortical cells (Rodney Douglas, University of Oxford) explains orientation selectivity rather well, including nearly all of the intracellular, extracellular, and pharmacological data on orientation tuning (Somers et al., 1995a). Interestingly, contrast gain control turns out to be a natural outcome of the model network based on the different properties of excitatory and inhibitory neurons (Sur). Christof Koch (Caltech) described how a similar model of recurrent excitation also works well for explaining direction selectivity; interestingly, while the model itself embodies feedback, and hence nonlinearity, its output is consistent with linear substrates for the generation of direction selectivity demonstrated experimentally (Ferster). The problem of direction selectivity is part of the broader, and neglected, issue of how time (at least relative time or delay between successive stimuli) is represented in the brain, as discussed by Horace Barlow (University of Cambridge). Barlow also reminded us that computation in the brain, as elsewhere, is a physical process. All the relevant parameters in computation have to be brought to a single place, a notion increasingly but dangerously neglected in discussing computations carried out by "neural networks."

The new models of orientation and direction selectivity are of much interest, for they represent clear, testable proposals for how cortical connections and microcircuits generate emergent new properties (e.g., Douglas et al., 1995). The role of long-range connections in primary visual cortex, which connect cells with similar orientation preference, can be explored systematically with computational models as well. Prior experiments have suggested both facilitatory and suppressive roles for long-range connections. Recent models and related experiments (Somers et al., 1995b) appear to resolve these apparently contradictory roles by showing that long-range connections can have either effect on the same cell population, depending on the level of local activation.

A long-standing problem in studying the receptive field properties of cortical neurons is how to evaluate their role in perceptual and motor behavior. One of the pioneers in tackling this problem (William Newsome, Stanford University) argued that in some circumstances it can be solved by correlating neuronal discharge and performance. By training monkeys to perform a two-alternative motion discrimination task and recording from cells in lateral intraparietal cortex, he demonstrated that the direction in which the animal made a saccadic eye movement in response to the perceived (and even remembered) direction of motion correlated with, and could be predicted from, the discharge of directionally selective neurons. By plotting the distribution of such neurons in extrastriate visual areas it should be possible to determine which areas are concerned with the perception of the direction of movement and which are concerned with other properties such as generating shape or depth from motion.

Information Processing and Transfer in Visual Cortical Areas

Two major questions were addressed at the meeting: to what extent is information processing in the visual system organized hierarchically or in parallel, and how is vision modulated by voluntary attention and integrated with information about eye movements?

There is strong anatomical and physiological evidence for three separate channels of information transfer from the retina through the lateral geniculate nucleus to visual cortex. These are called M (magnocellular), P (parvocellular), and K (koniocellular) channels. It has been demonstrated by electrophysiological and lesion studies that, although most stimuli activate all three channels, information about color and high spatial frequency is carried by the P channel, and high temporal frequency and low contrast information are carried by the M channel. It had been thought that the P and M channels remain separate in cortex (e.g., Livingstone and Hubel, 1987). The P pathway was supposed to separate into two branches through areas V1 and V2 toward area V4, one branch devoted to form and the other to color processing. The M pathway was thought to project through different territories in areas V1 and V2 to activate area MT and to be devoted to the processing of motion information.

The extent to which P and M channels contribute to coding in extrastriate visual areas was addressed by John Maunsell (Baylor University), in particular with respect to the extent of the segregation of P and M signals in the so-called ventral and dorsal processing streams, which appear to play such different roles in vision. By injecting a blocking agent into separate layers of the dLGN, it was possible selectively and reversibly to inactivate either the P or M channels for one eye and to examine the effect of this on the receptive field properties driven from that eye in extrastriate visual cortex. Neurons in area MT were found to depend almost entirely on signals from the M channel in that most of them became visually unresponsive when the magnocellular layer was inactivated; blocking the P channel had only a slight effect on most neurons in area MT. In contrast, and much more surprisingly, individual neurons in area V4 could be shown to receive a substantial input from both P and M channels, as do the cells in V1 that give rise to the ventral pathway. In some V4 cells, the entire excitatory input was provided by the M channel. Overall, the dorsal pathway, or at least that part deriving from area MT, has an overwhelmingly M-type input, whereas the ventral channel is a mixed bag.

How the above properties arise was discussed by Jennifer Lund (Institute of Ophthalmology, London), who de-

scribed the microanatomy of the M and P channels in areas V1 and V2. To the existing physiological evidence of a gradient of M to P properties from the top to the bottom of layer 4C can now be added evidence that it arises from the dendritic overlap of spiny stellate neurons with a similar ratio of M and P input. Three projection pathways are now known to emerge from layer 4C, each comprising both excitatory and inhibitory properties, and each of them is destined for a different layer above 4C, where the segregation is again accompanied by differences in physiological properties involving orientation and direction specificity and color coding. The intracortical lateral connections in V1 are predominantly between chemically and functionally similar compartments, for example, between cytochrome oxidase–rich blobs and between interblobs. However, the patterning of the lateral connectivity in V2 differs from that of V1, although it is not yet fully clear how this correlates with P and M channels.

The cerebral cortex is often discussed and investigated as if the cortical territories concerned with sensory processing were separate from those processing motor output. It is becoming clear that, within sensory cortex, there is far more integration between sensory and motor information than previously thought. Yves Trotter (Centre National de la Recherche Scientifique) showed that vergence movements of the eyes influence the processing of information by neurons of V1, the first cortical processing stage of visual information. Dris Boussaoud (INSERM) presented results demonstrating that information about eye movements and attention modulates the responses of neurons in visual cortex and, beyond, in frontal cortex and the basal ganglia.

Still within area V1, neural mechanisms of depth discrimination were described by Trotter. Although it is already well known that even as early as V1 single cells are exquisitely sensitive to the distance at which stereograms are presented in front of or behind the fixation plane, Trotter described experiments demonstrating that for 75% of such neurons their activation additionally depends on the actual distance at which a monkey fixates; i.e., for a given disparity, response also depends on viewing distance. It was possible to demonstrate that convergence angle is at least partly responsible for this phenomenon and that an extra retinal signal related to vergence must be integrated as early as area V1. Perhaps it is even earlier, in the thalamus!

The role of subcortical as well as cortical visual areas in processing visuomotor information was described by Boussaoud, who concentrated on the nucleus of the optic tract (NOT) and the superior colliculus (SC), both of which have well-established visuomotor roles. What has become clear is that the cortical projection from the superior temporal sulcus to the NOT interacts with the retinal input to the NOT to create the full array of visual response properties characteristic of the optokinetic reflex. In addition to cells whose activity is related to saccadic eye movements, the SC contains neurons that discharge before and during arm movements. The most recent work demonstrates two types of what can be called "reach cells." The first type discharges in similar fashion during movements to a visual target that follows a saccadic eye movement and when the monkey had to withhold such an eye movement while reaching for the target, which was therefore represented on the peripheral retina. The second and smaller group discharge only if the target is in a particular position on the screen. Before these cells discharge, they require a stimulus on a particular part of the retina and the act of moving the arm, and they are presumably part of a sensory to motor transformation.

Whether information is processed independently in separate areas or channels or whether it is distributed among several subunits (cortical areas or channels) is an age-old question that was at the core of many heated debates during the last century. This question of segregation versus integration of information within cortex was addressed by Giulio Tononi (Neurosciences Institute, La Jolla), who presented a more theoretical and computational approach to integration to account for the multiple levels at which interactions occur during perception. The most effective computer simulations of the connectivity and physiological properties of the visual system indicate that neuronal activity in segregated areas is integrated to provide a coherent percept in the absence of any "master" area. At least in general terms, such models provide a clue to the solution of the binding problem, i.e., how activity in segregated regions acquires the appropriate temporal patterning that signifies correlated rather than uncorrelated activity. The interplay between functional segregation and functional integration is referred to as neural complexity (CN), i.e., how much the increase in integration with increasing size of the subset deviates from linearity. CN is high in systems that conjoin local specialization with global integration and low when the components are either completely segregated or completely integrated. The known connectivity patterns of the cerebral cortex such as strong local connectivity, patchiness, and reciprocity are all associated with high values of CN. CN is now proving useful in exploring the significance of the evidence (described below) from functional neuroimaging that a patchwork of areas is usually involved in even the simplest perceptual task.

Human Visual Cortex

The chief problem in studying the human brain that was addressed at the meeting was that of identifying different functional regions in the human extrastriate visual cortex and, where possible, establishing their analogies and homologies with similar areas in monkeys and elucidating their role in vision. Balazs Gulyas (Karolinska Institute, Stockholm) reviewed the progress being made toward developing a computerized functional atlas of the human brain. He and his colleagues have superimposed the functional localization determined by positron emission tomography (PET) onto existing maps of the human cortex determined by cyto- and myeloarchitecture and the exciting new results obtained from receptor architecture. By standardizing in shape and size the magnetic resonance (MR) and PET images of human subjects participating in functional activation experiments with respect to visual perception, MR and PET images whose glucose and protein me-

tabolism was being measured, MR and PET images of patients with temporal lobe epilepsy whose $GABA_A$–benzodiazepine receptor distribution was measured, and postmortem brains stained for the distribution of various neurotransmitters, the author and his colleagues have produced a standardized and computerized brain atlas that, in theory, allows anatomical or functional images of any single brain to be transformed into the coordinates of the standard brain. For example, their investigations have revealed at least nine extrastriate visual areas in the occipital lobe that can now be compared to the well-known standardized maps that have been provided for the extrastriate cortex of macaque monkeys. Whether the entire venture amounts to a search for the holy grail was a matter of lively discussion.

Roger Tootell (Massachusetts General Hospital, Boston) demonstrated how functional MR imaging can be just as informative as PET, at least with respect to demonstrating human extrastriate visual areas, and in some respects superior to PET in that it can be carried out frequently and apparently noninvasively. By studying subjects who were required to inspect a variety of visual displays designed to activate the representation of the vertical retinal meridian (which demarcates the border between many extrastriate visual areas) or displays designed to activate regions concerned with specific cortical computations (such as registering movement or color), it was possible to distinguish ten different cortical visual areas, all of which can be related (but with different degrees of confidence) to well-known areas in the occipital lobe of macaque monkeys. Although some differences and problems remain unsettled (e.g., whether human V3 shows little selectivity for motion, whether the ventromedial "color" area corresponds to macaque area V4, and whether human area LO has any counterpart in the simian cortex), the similarities between the regional architecture of the occipital lobe of man and monkey are abundantly clear.

How the many extrastriate visual areas carry out their duties remains unclear and controversial. As Henry Kennedy pointed out in his introduction to the session on language, "nobody (barring MacMillan Press) really knows what the multiple visual areas are up to." Both Alan Cowey (University of Oxford) and Guy Orban (Katholieke University, Leuven) described investigations that bear on this issue, and both referred to experiments using PET in conjunction with a particular basic task, with the task difficulty titrated so that performance was similar across all variations of the task in order to equate variables that undoubtedly influence cerebral activation patterns. Orban used the orientation of visual stimuli as the main variable in perceptual tasks where subjects had to detect, discriminate, identify, compare, or passively view oriented stimuli. The results he described indicate that at least seven different extrastriate areas are involved in processing the orientation of a centrally viewed stimulus and that there is certainly no single "orientation" area. Instead, the occipital cortex appears to be working as a dynamic cluster of areas that interact, although there is still no incontrovertible evidence for the latter, and no one knows why seven areas are needed for such an apparently simple attribute as orientation. Cowey described the results of similar experiments carried out with colleagues in Stockholm. When subjects had to select the odd one out of three rectangular shapes on a screen and the shapes were created solely by luminance, isoluminant color, binocular disparity, or global motion, different and surprisingly nonoverlapping patterns of functional activation emerged in every case. These results also suggest that, even in what would be called a simple visual task—discriminating shape created by a single attribute—multiple and different cortical areas are involved. Cowey also described related experiments in which analogies between human and simian extrastriate visual areas were investigated by comparing the effects of localized brain damage on perceptual performance. Although the functional correspondence between area MT (and perhaps surrounding areas such as MST) of the simian cortex and a region of the human cortex now referred to as human V5, revealed by functional activation studies, is almost beyond question, some surprising anatomical mismatches remain. Perhaps the most puzzling concerns the region of the lingual and caudal fusiform gyri, which when damaged produce cerebral achromatopsia in neurological patients. Although now often referred to as human V4, it is mysterious why complete removal of area V4 in macaque monkeys leaves them essentially unimpaired on chromatic tasks that an achromatopsic patient finds impossible, and why removal of more rostral ventral temporal cortex in macaque monkeys does render them achromatopsic. Such inconsistencies will undoubtedly lead to further behavioral and neuroimaging studies.

Cortical Processing of Language

Henry Kennedy also noted in his introduction to the session on language that we have no anatomically and physiologically determined cortical map for language like that of the multiple visual areas in animals to guide our investigations, although he also hinted (tongue in cheek?) that perhaps this might help rather than hinder. Perhaps 20 years ago, and even now in some textbooks, the broad organization of language seemed straightforward. Within a region called Wernicke's area, the cortex dealt with the comprehension and initial production of language, whereas Broca's area was concerned with speaking, seen as a motor act. This neat bipartite division of labor belied the stunning complexity of language and the fact that possibly more of the human brain is devoted to language and its role in other perceptual and cognitive skills than to any other set of neural operations. One has only to sample the variety of disorders of language, whether acquired or developmental, to realize that however language is organized neurally it is unlikely to be less complex than vision.

Some of this complexity was described by Stanislas Dehaene (Laboratoire de Sciences Cognitives et Psycholinguistique, Paris), who has used PET successfully to disentangle the different cortical fields that are active during different levels of language processing. Phonology, prosody, lexical access, syntax, and semantics were all varied in order to uncover the many regional differences in activa-

tion. And there were surprises, such as the activation of the temporal poles by sentences with acceptable syntax and prosody. Of course, as the speaker admitted, such mapping studies on their own reveal little about mechanism, but this problem was partly overcome by combining PET with high density recording of event-related potentials (ERPs) in order to study the time course of activation of different processing mechanisms, and even of different areas. ERPs were also measured in babies as young as 2 months old to study language acquisition, and two stages of processing were identified, almost certainly corresponding to acoustical versus phonological processing. The results of measuring ERPs also indicate that young babies can identify a syllable in less than 400 ms, and that even at 2 months of age the left temporal lobe is already specialized for language processing.

ERPs, often in conjunction with functional MR imaging, were also discussed by Helen Neville (Salk Institute) in relation to studies of visual and language processing in normal hearing and congenitally deaf adults. Within both vision and language, there are distinct subsystems with different degrees of experience-dependent modification. Within vision, auditory deprivation affects the processing of visual information from the peripheral visual field. Within language, delayed exposure to language has marked effects on the development of grammatical processing but few effects on lexical skills. Deaf children have faster reaction times to visual stimuli in the peripheral visual field. But visual evoked potentials (VEPs) in response to changes in isoluminant chromatic gratings or to movement of achromatic gratings show that normal and deaf children have similar VEPs to the former (perhaps reflecting activity in occipitotemporal cortex), whereas achromatic gratings give much larger VEPs in dorsal occipitoparietal areas in deaf children. VEPs were also present in deaf children in areas of the lateral sulcus that would normally be classified as language areas, as were functional activations in the right parietal cortex in deaf subjects when using American sign language but not when reading text. The studies described by Neville demonstrate extensive plasticity in reorganization in the young human brain deprived of one of its major sensory inputs, but they also highlighted some puzzling differences in results obtained when localization is studied by the effect of lesions, by ERPs, or by functional MR imaging.

Some of the points raised by Neville were taken up by Elizabeth Bates (University of California, San Diego), who reviewed findings from infants with focal brain damage and adults with adult aphasia. Her principle conclusions are that linguistic representations are not innate and not localized, but that processes subserving language are innate and localized but not specific to language. The conclusion that linguistic representations are broadly distributed in the brain comes from several sources: individuals with expressive agrammatism, who have no deficits in the use of grammar to interpret sentences; demonstrations that receptive agrammatism is not specific to any particular lesions site and can be simulated in normals who are forced to process language under stress; patients with so-called agrammatic aphasia who can nevertheless make relatively fine-grained judgments of grammaticality; and cross-linguistic studies of adult aphasia, showing that much language-specific knowledge is preserved despite serious deficits in real-time processing. All these studies suggest that linguistic knowledge (especially grammar) is not regionally localized in the brain and that explanations for aphasic symptoms must lie instead in the distributed local processes by which knowledge is activated and deployed.

Insights into the nature of those localized processes come from studies of infants and children with left or right hemisphere injuries acquired before 6 months of age. These children do display initial deficits in language ability, showing that the brain is not equipotential for language. However, the nature of those initial deficits and the reorganization that follows suggest that the regional specialization for language is built upon local variations in computational style, variations that are only indirectly related to language content and do not map consistently onto lesion–behavior correlations in adults. Some surprising findings in infants include: evidence that very early comprehension and gesture are more affected by right hemisphere damage (the opposite of findings with adults!); evidence that expressive vocabulary is affected more by left temporal injuries throughout (but not beyond) the period from 10–60 months of age; related evidence that expressive grammar does not dissociate from vocabulary in this age range, and is also affected more by left temporal injuries; the existence of a brief and surprising period from 19–30 months when injuries to either left or right frontal areas produce marked delays in acquiring vocabulary and grammar; no evidence at any point in early development that left frontal areas play a privileged role; and finally, the complete disappearance of side- or site-specific effects after 5 years of age, when most children with early focal brain injury are performing within the normal range. One explanation for these complex findings draws on parallels between the deficits observed in early language and the deficits observed in the same children in visuospatial cognition, suggesting that regions of cortex are specialized for modes of information processing that have a similar effect in linguistic and nonlinguisitic domains. It is as if, during language learning, regions compete to "attract" the language task, and under default circumstances particular regions are more likely to succeed. But when default circumstances do not hold, a number of different forms of organization are possible, and most of them appear to work well.

Michael Gazzaniga (University of California, Davis) brought a heady session down to earth by drawing attention to possible problems that are rarely discussed, perhaps because they make us uncomfortable. Many of us rely on knowledge about the structure, chemistry, and functional organization of animal brains in order to discover how the human brain works. For some neuroscientists, this is the sole reason for working on the brains of animals. Gazzaniga argued that unusually large brains, like ours, might in part be large because they contain more

specialized circuits than the brains of animals, and perhaps even unique computational processes. While many might agree with the point of view he presented, most would probably argue that many computational processes in the human brain are not uniquely human (e.g., sensory representation up to and including primary sensory cortical areas). The question is where to draw the line between what is uniquely human and what is not, and no one had the answer, although language would probably receive the most votes. Nor was it clear how one should go about studying the neural basis of cognitive processes that might be uniquely human; for example, should we be following up the report that pyramidal cells are larger in language areas of the left hemisphere than in the right hemisphere, and how can we ever determine the structural and functional properties of canonical microcircuits of the human cerebral cortex? Perhaps these difficulties explain why many neuroscientists, even those concerned with cognition, prefer to work with brains whose structure and properties can be studied alongside their performance as manifested in behavior.

Conclusions

While many different aspects of cortex were featured at the meeting, the major emphasis was clearly on the visual cortex. This one-sidedness almost certainly reflects the fact that ideas and concepts from work on the visual cortex have set the pace for much subsequent work on other cortical areas. The visual cortex has been the subject of intense research in the last three decades, particularly after the Nobel Prize–winning discoveries by David Hubel and Torsten Wiesel that cells in the visual cortex respond selectively to bars of light at particular orientations, and that the visual cortex fails to respond to an eye deprived of vision shortly after birth. These ideas have shaped the field of cortical function and development, and their continued influence on the field was very much in evidence.

The specificity of neuronal responses in cortex presupposes a high degree of connectional specificity. The sequence of cortical development suggests a progressive restriction of connection choices with time. The earliest events in development of cortex proceed without the influence of electrical activity, and a major new trend is the recognition that, where previously exuberence and pruning of connections ruled, most axons arrive at the correct place and then grow to adult size without depending on activity generated by behavior. Later events, including the sharpening of thalamocortical and intracortical connections, require activity in thalamic afferents and cortical target cells. Hitherto unsuspected divergence and convergence of inputs to neurons remain, even in primary sensory areas of adult cortex. This provides the basis for rapid, context-dependent plasticity or cortical dynamics. Longer-term plasticity, such as after deafferentation or removal of peripheral sensory input, may also involve sprouting at different levels of the projection system, including subcortical stations. Adult cortical plasticity may provide the substrate for at least certain kinds of learning and acquisition of skills.

A specific example of an emergent property arising from a cortical network is orientation selectivity in visual cortex. Novel approaches, including a combination of modeling and experiment, have led to new proposals for the generation of orientation selectivity. The utility of such models is not only that they speak to longstanding questions about visual cortex but also that they have relevance for understanding general features of cortical connectivity and function. Every area of cortex has similar short-range excitatory connections, inhibition that balances excitation, and long-range connections that link neurons with common features. Perhaps the proposals for the function of these connections based on their role in orientation selectivity, which yield robust extraction of signal from noise and dependence of responses on stimulus context, will turn out to be general and indispensable features of cortical circuits.

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